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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/593,316	06/13/2000	John Clark	730/002	5627

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GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/593,316	CLARK ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) 7-32 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 13 June 2000 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the Examiner has not shown that a serious burden would be required to examine claims combined of groups I and II, or I and IV, or III and VII or V and VIII. In response, groups II and I will be rejoined and examined together in the instant Office action. The restriction to group IV is maintained because although groups IV and I could be related as product and process of use, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, xenotransplantation could be practiced with different cells and organs, and the claimed tissue, cells, and animals could be used in a materially different process other than xenotransplantation, such as developing cell lines, ex vivo organ culture, and animal breeding. These different processes have different method steps, modes of operation, criteria of measurement, use different starting materials, and have distinct technical considerations. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Concerning the Request for Rejoinder of Group IV pursuant to M.P.E.P. §821.04, the following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

> "However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with M.P.E.P. §821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of process claims with product claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

The request for traversal of groups III, V, VII, and VIII is irrelevant to the current prosecution, would be considered in the event a related divisional application is filed.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than

appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-32 are pending, however, claims 7-32 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-6 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications*

under 35 U.S.C. § 112, p 1 "Written Description" Requirement; Federal Register/ Vol. 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 1 recites "Ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants", claim 3 recites "isolated ovine cell or tissue that expresses glycosyl transferase enzymes but does not detectably express α(1,3)GT", claim 6 recites "an ovine animal that is homozygous for inactivation of an α1,3GT gene". In view of the breadth of the claims given the broadest reasonable interpretation, the claims embrace a genus of ovine tissue from any strain of sheep, having the characteristic of devoid of antibody-detectable Gal α (1,3)Gal determinants, or of detectable α (1,3)GT expression, by any methods, and a genus of different strains of ovine animals homozygous for inactivation of an α1,3GT gene. However, the only ovine tissue and animal described in the specification is Finn Dorset (FD) sheep by targeted disruption of α1,3GT gene.

Claim 4 recites "an ovine cell which is heterozygous or homozygous for inactivation of an α (1,3)GT gene". Claim 6 recites "an ovine animal that is homozygous for inactivation of an α1,3GT gene", Although the claims do not require a particular phenotype for the resulting cells of homozygous or heterozygous inactivation of the α1,3GT gene, in light of the specification, they embrace the requirement for the cell to be devoid of antibody-detectable Gal α(1,3)GT Gal determinants. However, the specification fails to teach whether the phenotype would be achieved in all strains of ovine by the method taught in the specification; and whether cells having heterozygous inactivation of α1,3GT gene would express such Gal determinants in FD sheeps.

In view of art-known methods of devoid of antibody-detectable Gal α (1,3)Gal determinants, *Edge* teaches (US 6,284,245) that Gal α (1,3)Gal epitope can be removed from the surface of a cell by a number of methods. The epitope can be cleaved from a cell surface by treatment of the cell with an α-galactosidase, by inhibiting α (1,3)GT activity, by antisense to α1,3GT gene, by treating cell with a chemical inhibitor of the enzyme, by a binding molecule to the epitope, etc. (2nd paragraph in column 6). *Hayashi et al* (Transplant Proc 1997;29:893) teach using adenoviral vector encoding antisense ribozyme to α1,3GT gene to inhibit α1,3GT gene expression to suppress hyperacute rejection to organ graft. Therefore, the recitations of claims 1 and 3 embrace many different cells and tissue devoid of antibody-detectable Gal α (1,3)Gal determinants.

In view of the state of the art in making a transgenic ovine animal and an ovine tissue having the phenotype of devoid of antibody-detectable Gal α (1,3)Gal determinants, it is still underdeveloped and highly unpredictable. *Linder* (Lab Animal 2001 May;30:34-9) teaches that the resulting phenotype of a targeted gene mutation would vary among different strains of animals, particularly the heterozygous recombination because the collective genes of the host would influence a trait. "THE PHENOTYPE OF MICE CARRYING A MODIFIED GENE WILL VARY DEPENDING ON THE GENETIC BACKGROUND BECAUSE OF THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME" (see entire article). Thus, the phenotype resulting from targeted disruption of α1,3GT gene in different strains would expect to be varied and unpredictable.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

In analyzing whether the written description requirement is met for the claimed subject matter as a genus of ovine tissue devoid of antibody-detectable Gal α (1,3)Gal determinants, a representative number of species has to be disclosed by their complete sequences, structure, and other relevant identifying characteristics, such as a reliable methods of making such (?). Considering the potential numbers of ovine tissue encompassed by the claims, the FD strain is not the representative species of the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* types and strains of ovine tissue and animals devoid of antibody-detectable Gal α (1,3)Gal determinants; it does not provide adequate written description for the broad class of *all* types and strains of ovine tissue and animals having homozygous or heterozygous inactivation of α1,3GT gene. Therefore, only the tissue and animal from FD sheep by homozygous recombination of α1,3GT gene meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for homozygous inactivation of α1,3GT gene in FD sheep, does not reasonably provide enablement for homozygous inactivation of α1,3GT gene in any strain of ovine; and it does not reasonably provide enablement for making ovine cells and tissue devoid of antibody-detectable Gal α (1,3)Gal determinants by homozygous or heterozygous inactivation of α1,3GT, in *any strain* of ovine. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different stains of transgenic animals is not consistent and varies according to the particular host genetic background.

Claims 1, 3, and 6 embrace a broad class of ovine animals, cells and tissue, from any strain of sheep, devoid of antibody-detectable Gal α (1,3)Gal determinants, or of detectable α1,3GT expression. However, the specification fails to disclose any other ovine animal apart from Finn Dorset (FD) sheep having such feature.

In view of the state of the art in making a transgenic ovine animal and an ovine tissue having the phenotype of devoid of antibody-detectable Gal α (1,3)Gal determinants, it is still underdeveloped and highly unpredictable. Although the technique of making transgenic and knock out animals has become routine in the relevant art, the resulting genotype and phenotype varies significantly depending on the genes being

manipulated, and the animals being used. The teaching of *Linder* supports the phenotype unpredictability in transgenic animals. *Linder* (Lab Animal 2001 May;30:34-9) teaches "THE GENETIC BACKGROUND AND THE SURROUNDING ENVIRONMENT ARE OFTEN OVERLOOKED PARAMETERS THAT CAN SIGNIFICANTLY AFFECT THE OBSERVED PHENOTYPE", "OTHER FACTORS INCLUDE MUTATIONS THAT ARE ACTUALLY HYPOMORPHS (I.E. MUTATIONS THAT CAUSE ONLY A PARTIAL DECREASE IN GENE EXPRESSION) RATHER THAN NULL ALLELES; COMPENSATORY PATHWAYS; AND TRANSGENESIS-SPECIFIC FACTORS, INCLUDING SITE OF INTEGRATION, TRANSGENE COPY NUMBER, AND INSERTIONAL MUTATIONS", "GENETIC BACKGROUND IS DEFINED AS A COLLECTION OF ALL GENES PRESENT IN AN ORGANISM THAT INFLUENCE A TRAIT OR TRAITS. WHILE MOST OF THE COMMONLY USED INBRED STRAINS SHARE A FAIRLY COMMON ORIGIN, EACH STRAIN HAS ITS OWN UNIQUE SET OF CHARACTERISTICS OR BACKGROUND LESIONS", "THE PHENOTYPE OF MICE CARRYING A MODIFIED GENE WILL VARY DEPENDING ON THE GENETIC BACKGROUND BECAUSE OF THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME" (see entire article). Thus, the phenotype resulting from targeted disruption of α1,3GT gene in different strains would expect to be varied and unpredictable. This unpredictability could be seen from the teaching of the specification that the skilled artisan fails to target α1,3GT gene in cells of black Welsh mountain sheep, the attempt is only successful in making the FD sheep.

Furthermore, for a recessive mutation, a mutant phenotype is only observed in homozygous allelic recombination. Even with homozygous inactivation of α1,3GT gene, the antibody response may not be devoid. This is supported by the teaching of *Tearle et al* (Transplant 1996; 61:13-9), they teach "WE HAVE GENERATED MICE LACKING THIS MAJOR XENOANTIGEN BY INACTIVATING THE α1,3GT GENE... SUBSTANTIALLY LESS XENOANTIBODY FROM

HUMAN SERUM BINDS TO CELLS AND TISSUES OF THESE MICE COMPARED WITH NORMAL MICE" (See abstract). *Tange et al* (Transplant Proc 1996;28:620-621) teach "GAL$^{-/-}$ MICE SHOWS AN APPROXIMATELY 60% REDUCTION COMPARED TO GAL$^{+/+}$ SPLENOCYTES". The specification fails to teach whether the cells from FD sheep having homozygous inactivation of α1,3GT gene is devoid of antibody-detectable Gal α (1,3)Gal determinants.

Claim 4 recites "an ovine cell which is heterozygous or homozygous for inactivation of an α1,3GT gene". However, the specification fails to teach whether the *heterozygous* inactivation of α1,3GT gene would lead to cells devoid of antibody detectable Gal α (1,3)Gal determinants in any and all strains of ovine , thus it is unclear how to use these cells. *Tange et al* (Transplant Proc 1996;28:620-621) teach "GAL$^{-/-}$ MICE LACK THE GAL EPITOPE, DETECTED BY LACK OF IB4 LECTIN STAINING ON PBLS, SPLENOCYTES, AND TISSUES. GAL$^{+/-}$ AND GAL$^{+/+}$ MICE BOTH SHOW IB4 STAINING ON PBLS AND ENDOTHELIA IN ALL ORGANS" (See Introduction). In view of such, the claim does not appear to be enabled in the absence of evidence to the contrary.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Conclusion

No claim is allowed. Claims 1-6 appear to be free of cited art of record, however, they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 16, 2001

JAMES KETTER
PRIMARY EXAMINER